CADTH

CADTH ISSUES IN EMERGING HEALTH TECHNOLOGIES

Informing Decisions About New Health Technologies

Issue 169 March 2018

Voretigene Neparvovec: An Emerging Gene Therapy for the Treatment of Inherited Blindness

CADTH

Authors: Utsav Patel, Michel Boucher, Louis de Léséleuc, Sarah Visintini.

Cite As: Voretigene neparvovec: an emerging gene therapy for the treatment of inherited blindness. Ottawa: CADTH; 2018 Mar. (CADTH issues in emerging health technologies; issue 169).

Acknowledgments: CADTH would like to acknowledge the contribution of Dr. David Maberley MD, FRCSC — Head, Department of Ophthalmology and Visual Sciences, University of British Columbia Faculty of Medicine — for his review of the draft version of this bulletin.

ISSN: 1488-6324 (English)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Summary

- Inherited retinal dystrophies (IRDs) are a major cause of early-onset blindness. Biallelic RPE65-mediated IRD, the most severe form of IRD, occurs when there are mutations in both alleles of the *RPE65* gene in retinal pigment epithelium (RPE) cells.
- Voretigene neparvovec, developed by Spark Therapeutics, Inc., Pennsylvania, US, is a gene therapy designed to deliver a normal copy of the *RPE65* gene to the RPE cells that are lacking a normally functioning *RPE65* gene.
- This is the first gene therapy that has completed a phase III clinical trial — a randomized, open-label, controlled trial assessing the safety and efficacy of voretigene neparvovec for the treatment of biallelic RPE65-mediated IRD.
- In the phase III trial, patients treated with voretigene neparvovec showed significant improvement in navigational ability in dimly light conditions, compared with the control group, at one year. This treatment was associated with mild to moderate ocular adverse events; one patient experienced a loss of visual acuity in the first assigned eye.
- Improvement in visual function appears to remain durable for up to three years based on current data. Longer-term safety and efficacy data for voretigene neparvovec are needed to confirm its duration of effect, its impact on retinal degeneration, and the impact on the quality of life of participants treated with this therapy.
- The US FDA approved voretigene neparvovec (voretigene neparvovec-rzyl as per the FDA label) on December 19, 2017 under the trade name Luxturna. The drug is also currently under review by the European Medicines Agency, with a decision expected in the latter half of 2018. In the US, the price of voretigene neparvovev-rzyl has been set to US$425,000 per eye (US$850,000 for bilateral disease); this is a one-time treatment.

Background

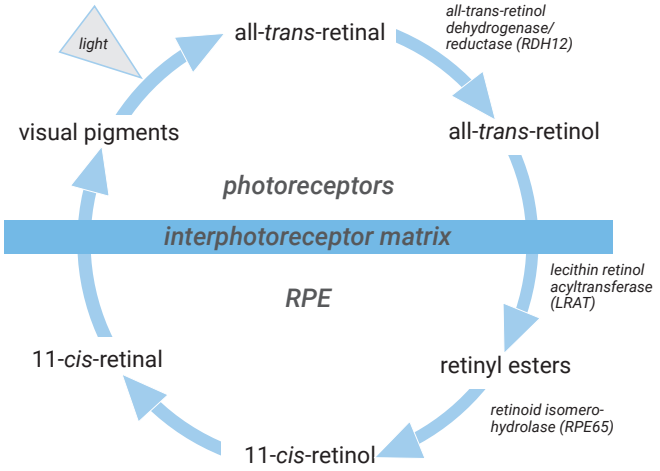
Inherited retinal dystrophies (IRDs) are a group of rare conditions affecting vision caused by mutations in any one of more than 220 different genes. These genes are crucial for retinal development and function.[1,2] The development and availability of genetic testing over the last decade have helped to identify the causative mutations for an increasing number of these conditions.[3-5] Effective treatments to reverse IRDs or slow their progression are currently unavailable.[6]

In patients with IRDs, visual impairment is caused when the light-sensitive photoreceptor cells in the retina malfunction. However, the clinical characteristics among individuals with this clinical diagnosis differ significantly. At the molecular level, most IRDs are the result of pathogenic changes in the DNA sequences of single genes. This monogenic etiology contrasts with that of retinal diseases, such as age-related macular degeneration, which have a multifactorial etiology.[7] The most common clinical subgroup of IRDs is retinitis pigmentosa — a disorder characterized by a reduced ability to perceive light and a progressive loss of visual field.[8] A less common but more severe IRD, Leber congenital amaurosis (LCA), is further characterized by earlier onset and more rapid progression of nyctalopia (the inability to see or perceive in dim light), and nystagmus (rapid involuntary movements of the eye).[9]

Monogenic diseases of the retina and the vitreous (the gel-like material that fills the middle of the eye) affect approximately one in 2,000 individuals, or more than two million people worldwide; however, the prevalence of LCA is lower at approximately one in 50,000.[8] A number of different IRDs are caused by mutations in *RPE65*, a gene expressed in retinal pigment epithelium (RPE) cells. Mutations in both alleles of the *RPE65* gene can cause LCA, and are responsible for approximately 6% to 16% of all LCAs.[7] The *RPE65* gene encodes all-trans-retinyl ester isomerase, also called RPE-specific 65 kDa protein or retinoid isomerohydrolase, or simply RPE65 enzyme. This enzyme is crucial to the visual cycle; it plays an important role in the regeneration of light-reacting proteins in the retinal photoreceptor cells (See Figure 1: Visual Cycle). As such, a functional RPE65 enzyme is required for

vision.[10] Those with LCA resulting from *RPE65* gene mutation are typically severely visually impaired or blind at birth, although some of these individuals will have their vision deteriorate later in life. Regardless, all are blind by young adulthood.[11] Other IRDs resulting from biallelic *RPE65* mutations include a form of retinitis pigmentosa called RP20 and severe early-childhood-onset retinal dystrophy (SECORD).[5,11,12] The exact prevalence of these latter disorders is unknown but they appear to be rare.

Figure 1: Visual Cycle



Source: reproduced with permission from den Hollander AI et al. Leber congenital amaurosis: genes, proteins and disease mechanisms. *Prog Retin Eye Res.* 2008:27(4):391-419.tv

The Technology

Gene therapy is an investigational approach to the treatment or prevention of genetic disease that seeks to augment, replace, or suppress one or more missing or mutated (malfunctioning) genes with functional gene copies. It addresses the root cause of an inherited disease by enabling the affected cells or organs to produce the normally functioning protein(s), or stop making the harmful protein(s), with the potential of bringing back normal function in the diseased cells or organs and slowing or reversing disease progression. A vector is used to transport the desired (functional) gene into the cell. The gene-vector pair can be delivered intravenously, injected into specific tissue, or incubated with cells outside of the body. The goal is to obtain, through a single intervention, a lasting therapeutic effect.[13]

Gene therapy has the potential to treat IRDs caused by biallelic *RPE65* mutations. A healthy *RPE65* gene can be introduced into the retina using a viral vector. The adeno-associated virus (AAV) has proven to have a vector with a favourable safety profile for many different types of gene therapy, as it does not cause any disease, cannot reproduce without a helper virus, and is less immunogenic than other viruses. In addition, the AAV can be manufactured to include only the genetic information to be transferred for gene therapy.[14] For the treatment of *RPE65*-dependent IRDs, AAV serotype 2 (AAV2) is used, since it can effectively infect RPE cells where RPE65 is usually expressed to induce prolonged levels of gene expression.[15]

Gene therapy with AAV2 does not repair or eliminate the defective gene but rather introduces a normal copy of the gene into the cell as free-floating DNA outside of the chromosomes.[16] The complex and evolving technology for gene therapy, the lifelong nature of genetic diseases, and the small patient populations available for trials make it difficult to establish the long-term safety and efficacy of gene therapy.[17,18]

Two distinct routes of administration, subretinal injection and intravitreal injection, can deliver a gene therapy vector to the retina. Of note, the subretinal space is the space between RPE cells and photoreceptors. While injecting materials into the subretinal space provides direct contact of the injected material with the plasma membrane of the photoreceptor and RPE cells, subretinal injection has only relatively been recently introduced in the clinical setting and requires specialized skills on the part of the clinician.[19] Whereas subretinal injection is a more complex operative procedure than that of intravitreal injection, the latter remains an invasive procedure. Despite the greater ease of administration, intravitreal delivery of AAV has had less success than subretinal vectors in animal models of outer retinal disease. This is likely related to the physical barriers required for the virus to access the outer retina, as well as the dilution of the vector within the vitreous cavity.[7]

Voretigene neparvovec (AAV2-hRPE65v2), a gene replacement therapy, consists of an AAV2 viral vector containing the human *RPE65* cDNA with a modified Kozak sequence under the control of a chicken beta-actin promoter with a cytomegalovirus (CMV) enhancer. It introduces the *RPE65* gene in the RPE cells and induces them to produce a functional enzyme. Administration of voretigene neparvovec by subretinal injection was found to improve the navigational abilities of patients with biallelic *RPE65* mutation in a phase III trial published in 2017.[1]

Regulatory Status

Voretigene neparvovec is manufactured by Spark Therapeutics (Philadelphia, Pennsylvania, US).[20] The US FDA approved voretigene neparvovec (voretigene neparvovec-rzyl as per the

FDA label) on December 19, 2017 under the trade name Luxturna. This one-time gene therapy product is indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Voretigene neparvovec-rzyl should only be administered to patients with mutations on both copies of the *RPE65* gene who have sufficient viable retinal cells, as determined by their treating physicians. Of note, this drug product is the first FDA-approved gene therapy for a genetic disease and the first pharmacologic treatment for an IRD approved in the U.S.[21]

The European Medicines Agency (EMA) is currently reviewing a marketing application for voretigene neparvovec for the European Union, with an expected action in the latter half of 2018. Spark Therapeutics is evaluating the regulatory pathway of other countries. At this time, the manufacturer has no plans to submit an application and commercialize voretigene neparvovec in Canada (Paul J. Savidge, Spark Therapeutics, Inc., Philadelphia, Pennsylvania: personal communication, 2017 Nov 27). Of interest, on January 25, 2018, Novartis bought rights to Spark Therapeutics to commercialize voretigene neparvovec outside of the US; the deal was worth USD $ 170 million. Spark Therapeutics will continue to exclusively commercialize voretigene neparvovec-ryzl in the US. As part of the deal, Spark Therapeutics will retain the regulatory responsibility for obtaining EMA approval for voretigene neparvovec; as stated above, the latter is currently under review at EMA for patients with vision loss due to LCA or retinitis pigmentosa caused by confirmed biallelic RPE65 mutations.[22]

Patient Group

LCA is a severe IRD in terms of visual loss and has a very early age of onset (less than one year of age).[8] In their first year of life, affected individuals usually experience profound blindness, roving nystagmus, abnormalities of the retina, and occasionally other symptoms.[23] LCA is known to involve at least six genes and, to add further complexity, different mutations in several of these genes can cause retinitis pigmentosa and other retinal dystrophies. Therefore, it has been suggested that LCA is the most severe condition that can result from mutations in these genes.[23] LCA patients bearing *RPE65* loss of function are classified under the LCA2 clinical subgroup, which accounts for 6% to 16% of all LCA cases. Individuals with LCA2 can experience visual impairment at a range of ages, from infancy to adolescence, and they most commonly develop night blindness at an early age.[24]

Spark Therapeutics recently provided estimates of the prevalent population of individuals with biallelic *RPE65* mutations. Based on epidemiology data from markets of interest to them — i.e., the US, Europe, and select additional markets in the Americas and Asia/Pacific — the company estimated this population to be approximately 6,000 individuals. Spark Therapeutics also estimated that between 1,000 to 2,000 people in the US have vision loss due to these biallelic *RPE65* mutations.[21] As Canada is approximately 10 times less populated than the US, it may be extrapolated that 100 to 200 Canadians could be candidates for therapy with voretigene neparvovec.

Current Practice

The notable genetic heterogeneity of LCA makes it a complicated disease to study and treat.[25] Before the approval of voretigene neparvovec in the US, there was no approved pharmacological treatment available for biallelic *RPE65*-mediated retinal dystrophy.[26] The American Academy of Ophthalmology has provided recommendations on genetic testing and screening.[27] Up until recently, treatment of IRDs was limited to routine physician visits and supportive care such as the use of low-vision aids, and orientation and mobility training.[6,26]

The Evidence

A limited literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, Scopus, and the Cochrane Library (2017, Issue 10). Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters). No filters were applied to limit the retrieval by study type. The search was limited to English-language documents published between January 1, 2012 and November 10, 2017. Regular alerts updated the search until project completion; only citations retrieved before January 8, 2018 were incorporated into the analysis.

The efficacy and safety of voretigene neparvovec were assessed in two open-label phase I trials, and one open-label, randomized, controlled phase III trial.[20] The phase III trial included 31 participants between the ages of four and 44 with genetic diagnosis of biallelic *RPE65* gene mutation and sufficient viable retinal cells. Participant vision impairment at baseline was measured for visual acuity and visual field. Participants with exposure to previous gene therapy, investigational drugs, and high-dose retinol compounds in the past 18 months were excluded. The primary efficacy end point was change in bilateral multi-luminance mobility test (MLMT) performance at one year, compared to baseline. The MLMT is a measure of functional vision at specified light levels. The MLMT is a task that challenges a subject to navigate a course (out of 12 standardized courses) at different light conditions, within a time limit. Each light condition was assigned a score ranging between 0 and 6; a positive change score indicates passing the MLMT at a lower light level. This test was developed by the manufacturer to assess the

navigational ability of trial participants. Secondary outcomes assessed visual and retinal functions using a full-field light sensitivity threshold (FST) test, MLMT of the assigned first eye, and best-corrected visual acuity (BCVA) averaged over both eyes.

Out of 31 participants, 20 received the intervention and nine were in the control arm. One participant from each arm discontinued the study prior to intervention but after randomization. All 31 participants were included in intention-to-treat analyses.[1,28]

Table 1: Summary of Phase III Open-Label Randomized Controlled Study (Russell et al., US, 2017)[1]

Study Design; Study Duration	Population at Baseline	Intervention and Comparator
Phase III, open-label, multi-centre, randomized (2:1 intervention to control) controlled trial 1-year primary end point	N = 31 Mean age: 15.1 years Age groups: < 10 years: 42% ≥ 10 years: 58% Baseline MLMT passing level (% subjects): < 125 lux: 52% ≥ 125 lux: 48%	Intervention: Voretigene neparvovec N = 21 1.5 x 10^{11} vg /0.3 mL subretinal injection Control:[a] N = 10
Results		
Primary end point: Bilateral MLMT score change at year 1 compared with baseline (ITT population) • Mean change (SD) both eyes: o Intervention: 1.8 (1.1) vs Control: 0.2 (1.0) o Difference (95% CI): 1.6 (0.72 to 2.41), *P* = 0.0013		
Secondary end points: • Mean FST (white light [reported as log 10 (cd.s/m²)] averaged over both eyes) o Difference: −2.11 (95% CI −3.19 to −1.04) between intervention and control groups (ITT), (*P* = 0.0004) • MLMT first eye score change at year 1 compared with baseline (ITT population) — Mean change (SD) first eye: o Intervention: 1.9 (1.2) vs Control: 0.2 (0.6) o Difference (95% CI): 1.7 (0.89 to 2.52), *P* = 0.0005 • BCVA mean change across both eyes at year 1 compared with baseline (ITT population) o Intervention: decreased by 0.16 LogMAR; Control: increased by 0.01 LogMAR o Difference (95% CI) −0.16 LogMAR (−0.41 to 0.08), *P* = 0.17		
Additional efficacy end points: • Goldman visual field, sum total degrees: Mean (SD): Intervention: 673.9 (423.7) vs Control: 397.8 (367.3) Difference at 1 year (95% CI) intervention to control: 378.7 (145.5 to 612.0), *P* = 0.0059 • Humphrey visual field: o Foveal sensitivity (dB): Mean (SD): Intervention: 25.8 (9.1) vs Control: 21.5 (8.9) Difference at 1 year (95% CI) intervention to control: 0.04 (−7.01 to 7.2), *P* = 0.18 o Macula threshold (dB): Mean (SD): Intervention 24.0 (8.0) vs Control: 15.8 (7.4) Difference at 1 year (95% CI) intervention to control: 7.9 (3.5 to 12.2), *P* = 0.0005		

[a] Eligible to receive voretigene neparvovec after one year.

BCVA = best-corrected visual acuity; CI = confidence interval, dB = decibel; FST = full-field light sensitivity threshold; MLMT = multi-luminance mobility test; SD = standard deviation; vg = vector genomes; vs = versus.

Improvement in both navigational abilities and light sensitivity were evident within the first 30 days after subretinal injection (one injection in each eye separately; these were administered 12 ± 6 days apart).These visual improvements persisted throughout the one-year follow-up (Table 1). The most common ocular adverse events were mild ocular inflammation, transient elevated intraocular pressure, and intraoperative retinal tears.

Thus, this study showed that a subretinal injection of voretigene neparvovec, compared with standard care, leads to a statistically and clinically significant improvement in navigational ability (a function of visual acuity, visual field, and light sensitivity), under bright or dim lighting conditions, in patients with *RPE65*-mediated IRD. Of interest, one patient experienced a loss of visual acuity in the first assigned eye. As indicated in Table 1, a non-statistically significant reduction in BCVA was observed in the intervention group. For the modified ITT population — i.e., a population that excluded any participant removed from the trial on the day of randomization and before any intervention — using the scale adapted from Lange et al. for off-chart acuities, intervention participants showed a significant 9.0 letter improvement versus a 1.6 letter improvement in control subjects averaged over both eyes (difference of 7.4 letters, 95% CI 0.1 to 14.6, post hoc P = 0.0469). This post hoc visual acuity analysis was requested by regulators and by the study data safety monitoring board.[1]

While the results reported in the phase III trial extend to one year, authors indicated that data supporting efficacy up to three years are available from the phase I trials.[1] Data on functional visual improvement (MLMT and FST) were recently presented as an abstract in a conference.[29] An assessment of the impact of this therapy on quality of life was not found in the published literature. However, the briefing document presented by Spark Therapeutics to the FDA[28] mentions two additional measurements of patient-related outcomes. A visual function questionnaire was used to evaluate the activities of daily living that are dependent on vision. Scores were averaged over 25 answers to questions rated 1 to 10; a high score indicating good performance. After one year, subjects reported an increase of 2.6 points, while controls improved by only 0.1 point (a difference of 2.4 points, 95% CI 1.0 to 3.8, P = 0.001).[30] In addition, community-based functional vision (or orientation and mobility) was independently assessed and recorded in a qualitative report of the "real-world" experience of participants. However, these data were not presented in the FDA report.[28,30]

Key limitations:

The phase III randomized trial bears a few key limitations. In particular, the trial has a very small sample size (N = 31); however, this needs to be considered in view of the rarity of the condition being treated. With respect to using an open-label study design, which may introduce bias compared with using a double-blind study design, a consideration may be that awareness of the intervention by patients and care providers in this study may have minimal consequences, as neither patients' nor care providers' behaviour would be expected to influence visual outcomes. Furthermore, risks associated with subretinal injection may have precluded the acceptability of a sham procedure in the control group.

The method used in the study to define baseline vision impairment is not routinely used by clinicians; the primary end point was developed by the manufacturer to assess functional vision following consultation with the FDA,[28] but this end point is not used to monitor vision improvement in clinical practice. Further, baseline vision impairment was imbalanced between the intervention and control arms; it is not clear if this imbalance affected outcomes. In addition, there is very limited evidence on the impact of voretigene neparvovec on the quality of life and the level of autonomy of the patients, including the ability to safely perform routine daily activities. As the manufacturer is planning to follow study patients for up to 15 years,[28] more information will become available on the treatment effects and the population that may benefit the most from this therapy.

Overall, currently available evidence indicates that, compared with standard care, a single subretinal injection of voretigene neparvovec administered in each eye of patients with biallelic *RPE65*-mediated IRD improves vision and navigability under different light conditions. Data from the phase III trial indicate that these improvements persist for up to two years following drug injection; three years accounting for phase I data.[1,6,20,29,31]

Adverse Events

Two ocular serious adverse events were reported in clinical trials:

- bacterial endophthalmitis, leading to increased intraocular pressure and subsequent optic atrophy in a phase I study patient
- sustained reduction in visual acuity in a phase III study patient.

The latter event was related to the surgical procedure.[20] Of note, the Luxturna prescribing information in the US includes specific warnings about these serious ocular adverse events.[32]

In the phase III study[1], the most common ocular adverse events were generally categorized as mild in nature:

- increased intraocular pressure (20%)
- cataract (15%)

- retinal tear (10%)
- eye inflammation (10%).

While the adverse events appear to be mild to moderate in severity, and related to the relatively complex administration procedure, the long-term risk of serious adverse events remains unclear because of limited data.[1,6]

Administration and Costs

The dosage used in the phase III trial and included in the approved US label consists of a subretinal injection of 1.5 x 10^{11} vector genomes (vg) of voretigene neparvovec (with a total volume of 0.3 mL).[1,32] The drug is to be administered in each eye on separate days;[32] in the phase III study, both eyes were treated 12 ± 6 days apart.[1]

The subretinal injection delivery of voretigene neparvovec places viral vectors in close proximity to the cell types of interest. Also, the sequenced delivery approach minimizes the risk to participants by allowing one eye to be treated at a time, enabling identification of any early harm occurring in the treated eye before administrating the drug in the other eye.[7]

No Canadian health care system–based economic analysis of voretigene neparvovec was identified. The US list price for voretigene neparvovec-rzyl has been set to US$425,000 per eye as a one-time therapy (US$ 850,000 for both eyes).[33] Using this figure, the Institute for Clinical and Economic Review in the US recently conducted an economic analysis. Authors of this report indicated that, using conventional cost-effectiveness thresholds, the high cost of voretigene neparvovec is unlikely to make this drug cost-effective for US health care. However, adoption of a societal perspective for the younger population (i.e., for those younger than three years of age) could make this drug cost-effective at a willingness-to-pay threshold of US$150,000/quality-adjusted life-year.[30] It remains to be seen whether this conclusion would hold in a Canadian context should the therapy be marketed in this country.

The manufacturer is currently developing programs to improve patient access to this expensive treatment.[34] These programs would feature arrangements with payers to spread payment over multiple years. They would also offer risk-sharing by paying rebates to health insurers should positive outcomes not be sustained over the long term.[34]

Concurrent Developments

A few other gene- or cell-based interventions for ophthalmic disorders in clinical development have been identified. Following is a sample of such interventions:

- A gene therapy similar to voretigene neparvovec is in development by MeiraGTx. The company has designed an optimized vector system for introducing a healthy copy of the human *RPE65* gene (AAV2/5-OPTIRPE65).[35] This investigational therapy has received Rare Pediatric Disease designation by the US FDA and will be studied in the treatment of LCA due to *RPE65* loss in a phase I/II clinical trial.[36]
- Intravitreal injection of ocular gene therapies may address some of the complexity, costs, and safety concerns of subretinal injections. AAV vectors designed for intravitreal injection are in early clinical investigation.[37]
- Delivery of the gene for ciliary neurotrophic factor by an AAV-based vector to achieve sustained anatomic and functional photoreceptor rescue for the treatment of retinitis pigmentosa is currently under investigation.[7]
- Stem cell therapies are currently being studied for IRDs and age-related macular degeneration given their potential to replace diseased cell types and restore visual function. Extensive efforts are underway to generate stem cell–derived photoreceptor cells, and preclinical models have shown initial success in visual restoration.[7]
- Photoreceptor cell transplantation in animals has been studied with ongoing trials.[38]
- Lenadogene nolparvovec (rAAV2-ND4), a gene therapy construct from GenSight Biologics, has been studied in a phase II trial for the treatment of Leber hereditary optic neuropathy[39] and is currently being evaluated in two phase III clinical trials.[40]

Other advanced interventions have recently been introduced to clinical practice in the area of ophthalmology, including retinal prostheses — implantable devices that, in the absence of functioning photoreceptors, transform photic information into electrical stimulation of the remaining retina such that signals are carried by the optic nerve to the brain.[7] Two such technologies are currently approved for clinical use in some countries. The epiretinal Argus II retinal implant (Second Sight Medical Products; California) was approved by the FDA in 2013 as a humanitarian device for patients with advanced retinitis pigmentosa. The Argus II and a subretinal prosthesis (Retina Implant Alpha-IMS; Retina Implant AG; Germany) are approved for use in Europe. Individuals who have received these and other implants in clinical trials had severe retinitis pigmentosa and possessed vision no better than bare light perception at baseline. Functional outcomes reported from these trials were varied and included improvement in aspects of visual function including shape recognition, target finding, and navigation.[7]

Like voretigene neparvovec, these new technologies still bear some challenges regarding the need for further data on clinical

efficacy and safety, as well as reimbursement and access, given their anticipated high cost. It will be important to tailor the selection of these technologies to the needs of patients.[6,7] Also, given their anticipated high cost, it will be important to determine the best candidates for these therapies.

Rate of Technology Diffusion

It is estimated that there are approximately 3,500 individuals with *RPE65*-mediated IRDs in the US and the five major EU markets (Germany, France, Italy, Spain, and the UK). Approximately 50% (1,750) of these patients are in the US alone.[6] The latter estimate is aligned with the manufacturer's estimate; i.e., between 1,000 to 2,000 persons in the US have vision loss due to biallelic *RPE65* mutations.[21] As such, the rate of diffusion of voretigene neparvovec will be limited to specific subpopulations. No epidemiological data on the number of Canadians affected by IRDs were found. However, given the much smaller Canadian population compared with the US, the rate of technology diffusion in Canada would also be expected to be small.

Implementation Issues

A number of implementation issues are foreseeable, should this new technology reach clinical practice. Following is a description of the key potential implementation issues.

Limited data on efficacy and safety:

- The duration of effect of voretigene neparvovec is currently unknown. Current evidence provides up to three-year follow-up data on certain treated individuals;[1,29] however, how long the effect lasts remains an unanswered question. Of note, the manufacturer is planning to follow all study subjects for 15 years for safety and efficacy.[28]
- Another research group evaluated a distinct *RPE65* gene therapy and indicated that it did not affect the progressive nature of retinal degeneration.[41] However, it is unknown whether voretigene neparvovec has the potential to reduce or eliminate retinal degeneration in IRD.[30]
- In view of abovementioned, a long-term follow-up of patients will be necessary to determine the persistence of functional improvement and to evaluate the effect of treatment on retinal degeneration.

Cost and coverage:

- It is difficult to estimate the economic value of voretigene neparvovec because of a number of unanswered questions. For example, there is still limited knowledge of the natural history of *RPE65*-mediated IRDs. There is also a lack of standard and clinically meaningful outcome assessment tools to study treatments for these conditions. Also, as previously mentioned, the recent Institute for Clinical and Economic Review report indicated that this gene therapy is not likely to be cost-effective from the perspective of the US health care system, though it could be cost-effective for the younger population using a societal perspective.[30] No information on the economic value and the quality-of-life impact of voretigene neparvovec in Canada could be retrieved.
- Of note, given the anticipated high cost of voretigene neparvovec in Canada, the availability of public and private coverage of this gene therapy could significantly affect access to treatment.
- Because of the unprecedented nature of gene therapy, most notably the high upfront cost related to a single treatment, some international payers are exploring novel funding mechanisms, including outcomes-based agreements and amortization schemes, to mitigate risks and ensure equitable access.[18] Whether these approaches would be applicable in a Canadian publicly funded health care system remains to be determined.

Complexity of procedure:

- Given the genetic nature of both the disease and the treatment, as well as the high cost of therapy, patients will have to have received a proper genetic and physical workup in order to be considered for treatment with voretigene neparvovec. These would include identification of the genetic etiology of their retinal disease (as the therapy would only target *RPE65* deficiency), and determining if target eyes contain sufficient viable retinal cells.
- The nature of the injection to administer this gene therapy — i.e., subretinal injection — may be a limiting factor given the skills required for using this administration route. Likely for this reason, the manufacturer indicated that voretigene neparvovec will be available only in a limited number of US Centers of Excellence that specialize in IRD, and that it will offer special training to clinicians for performing the procedure.[21,28] Should voretigene neparvovec be eventually marketed in Canada, there might also be benefits in limiting access to a few dedicated Canadian injection sites. Although such an approach may be needed for ensuring quality of care, some patients may face logistical challenges to access treatment.

Although the overall impact of voretigene neparvovec on productivity has not yet been studied, it can be postulated that improvements in independence, mobility, and overall visual function may expand the range of employment options open to individuals with biallelic *RPE65*-mediated IRD and increase their ability to participate in social activities.[42] Formal validation will, however, be required to confirm such potential societal impacts.

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